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WILEY

ORIGINAL ARTICLE

HbA1c response after insulin initiation in patients with type 2 diabetes mellitus in real life practice: Identifying distinct subgroups

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Aims: To identify subgroups of patients with type 2 diabetes mellitus (T2DM) following distinct trajectories of HbA1c after insulin initiation and explore underlying differences in clinical characteristics.

Materials and methods: A cohort study was conducted in patients with T2DM initiating insulin in 2007–2013 with a follow-up of 2 to 4 years. Data were collected from the Groningen Initiative to Analyze Type 2 Diabetes Treatment (GIANTT) database. The primary outcome was subgroups with different trajectories of HbA1c patterns after insulin initiation, as identified by latent class growth modeling. Differences between subgroups were tested using one-way ANOVA, Kruskal-Wallis or chi-square tests, where appropriate.

Results: From 1459 patients, three subgroups with distinct HbA1c patterns were identified. Group 1 (8%) initially showed a moderate decrease followed by an increase in HbA1c 2 years later, despite receiving more comedication. Group 2 (84%) showed a stable decrease. Group 3 (8%) had a high initial level of HbA1c and a rapid decline within the first year, followed by a slow increase thereafter. Group 1 patients were on average 6–7 years younger than patients in groups 2 and 3 and were more likely to receive sulfonylureas than Group 3 patients. Group 3 patients had a shorter diabetes duration and were less well-controlled for HbA1c, systolic blood pressure and LDL-cholesterol at insulin initiation.

Conclusions: Most patients showed a stable HbA1c response, but one out of six patients showed either a poor response, or a rapid initial response only after insulin initiation. Response patterns were associated with age, diabetes duration and risk-factor controls at the time of insulin initiation.

KEYWORDS

antidiabetic drug, glycaemic control, insulin therapy, observational study, primary care, type 2 diabetes

1 | INTRODUCTION

In people with type 2 diabetes mellitus (T2DM), insulin replacement therapy is recommended when oral therapy alone is no longer sufficient to maintain glucose levels, or when oral drugs cause unwanted side effects.[1] Due to the complexity of insulin treatment and also patients' heterogeneity, the decision to switch to insulin is made based on patients' individual needs as well as physicians' judgements.[2] Observational studies show that 15%-24% of people with T2DM will receive insulin in the course of their treatment.[3–5] Yet individual

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responses to insulin treatment vary.[6] Several studies show that the short-term glycemic response to insulin initiation is strongly dependent on baseline HbA1c level, and to a lesser extent on body mass index (BMI) and duration of diabetes.[7,8]

A recent Dutch study looked at HbA1c response after insulin initiation over a mean follow-up period of 5.6 years and identified four different subgroups, each following distinct trajectories of changes in HbA1c over time.[9] Patients in the subgroups were different in a number of characteristics such as age, systolic blood pressure (SBP) and renal function, suggesting the existence of differential response phenotypes. However, one of the study's limitations was that the patients were all managed in a centrally organized care system that is not representative of routine diabetes care. Therefore, this study seeks confirmation in a population with T2DM which is more representative of routine primary care practice.

The aim of this study is to identify subgroups of patients with T2DM following distinct trajectories of HbA1c after insulin initiation. In addition, this study aims to describe and compare clinical characteristics of the subgroups. The findings of this study may guide individualized treatment decisions regarding initiation and management of insulin treatment in clinical practice.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

A population-based study was conducted in a large dynamic cohort of patients diagnosed with T2DM treated in Dutch routine primary care between 2007 and 2013.

2.2 | Data source

Data were collected from the Groningen Initiative to Analyze Type 2 Diabetes Treatment (GIANTT) database.[10] This longitudinal database contains anonymized data extracted from the electronic medical records of virtually every patient with T2DM (<1% opted out) managed by routine general practice in the north of The Netherlands.[11] Patients can enter the cohort when they are newly diagnosed or when they move into the area with a diagnosis of type 2 diabetes. Patients can leave the cohort when they move out of the area, when they are no longer being treated in primary care, or when they die. The GIANTT database includes prescription data, medical histories, results from routine laboratory tests, and physical examinations from over 50 000 patients diagnosed with T2DM. The GIANTT database has been extensively described and validated and has been used previously in over 40 studies.[11]

2.3 | Population inclusion criteria

Patients were included if they initiated insulin treatment between January 1, 2007 and December 31, 2013. The recommended treatment target in this study period was HbA1c < 53 mmol/mol. In addition, patients needed to meet the criteria for inclusion by having:

(1) at least one HbA1c measurement taken within 365 days of the preceding insulin initiation;

(2) insulin prescribed within 365 days before each follow-up HbA1c measurement to ensure that insulin was not discontinued in the follow-up period;

(3) been present in the cohort for at least two, and a maximum of 4 years, to allow for similar follow-up periods in this dynamic cohort; and.

(4) at least four HbA1c measurements in the follow-up period.

2.4 | Baseline characteristics

Data on patient characteristics were collected at baseline (i.e. the date of insulin initiation) on age, sex, duration of diabetes (≥2 years), and the latest values taken from laboratory tests and physical examinations within 365 days prior to insulin initiation of HbA1c, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, SBP, albuminuria (yes/no), estimated glomerular filtration rate (eGFR), BMI and smoking status. Also included were the numbers of patients with prescriptions for oral glucose-lowering drugs (such as metformin, sulfonylureas, acarbose, thiazolidines and dipeptidyl-peptidase-4-inhibitors) where the duration overlapped with the date of insulin initiation, those with histories of cardiovascular disease (ICPC-1 codes: K74, K75, K76, K77, K83, K84, K89, K90, left ventricular hypertrophy, coronary artery bypass graft, percutaneous transluminal coronary angioplasty), peripheral vascular disease (ICPC-1 codes: K91, K92, K99.1, K99.6, F83, N94.2, and text-derived codes for peripheral bypass, percutaneous transluminal angioplasty, diabetes nephropathy, diabetes foot), renal disease (ICPC-1 codes: U85, U88, U90, U99.1,2,3), malignancy (ICPC-1 codes: A79, B72, B73, B74, D74, D75, D76, D77, F74.1, H75.1, K72.1, L71.1, N74, R84, R85, S77, T71, U75, U76, U77, X75, X76, X77, Y77, Y78) and psychological conditions (ICPC-1 codes: P77–P99). The cut-off point for diabetes duration was chosen to distinguish patients who were recently diagnosed with T2DM (diabetes duration <2 years) from those who had diabetes for a longer period (≥2 years). (The records of patients with a diabetes duration of <2 years were manually checked for possible misclassification by either the date or the diagnosis, but no obvious misclassifications were identified.) Albuminuria was defined as being present (yes) if the albumin-to-creatinine ratio (ACR) was ≥2.5 mg/mmol for males and ≥ 3.5 mg/mmol for females. Values of eGFR were calculated from the baseline values of serum creatinine using the CKD-EPI formula.[12]

2.5 | Follow-up

For each 6-months period during the follow-up the following data were collected: the number of patients having at least one HbA1c test, the total number of HbA1c tests which took place in the preceding 90 days, the number of patients with an insulin prescription in the preceding 90 days and the type of insulin prescribed, the number of patients with prescriptions for oral glucose-lowering drugs (such as metformin, sulfonylureas, acarbose, thiazolidines and dipeptidyl-peptidase-4-inhibitors) where the duration overlapped each 6-months time point, and the number of patients without any prescriptions for glucose-lowering drugs.

2.6 | Statistical analysis

Subgroups of patients following distinct trajectories of change in HbA1c over time after insulin initiation were identified using latent class growth modeling (LCGM).[13] Briefly, LCGM is a technique used to identify distinct subgroups of individuals following similar patterns of change over time on a given variable. Although each individual has a unique developmental course, the heterogeneity in the distribution of individual differences by changes within the data is summarized by a set of polynomial functions, each of which corresponds to a distinct trajectory.

The LCGM analysis was performed in Mplus 7.4. The trajectories were modeled using a modified version of example 8.1 from the Mplus user's guide.[14] Linear, quadratic and cubic generalized method of moments (GMM) were modeled using only HbA1c values (no covariates) in a similar way to Mast et al.[9] The model fit indices were compared and results of the cubic models with fixed quadratic and cubic slope variance across trajectories were presented. The default (unstructured) variance–covariance structure was assumed to mean that each time point has its own residual variance, and that residuals are uncorrelated across time. The graph was plotted in Stata 14.1. The optimal number of subgroups was determined using a stepwise approach. The number of subgroups increased by one if all of these criteria were satisfied:

(1) the model fit (assessed by Bayesian information criterion [BIC]) improved and the difference between the models ($2 \times$ [BIC model 1 − BIC model 2]) was $>10^{13}$;

(2) the number of patients in the newly determined subgroup is >1% of the total population; and.

(3) the model converges (the best log likelihood has been replicated).

The differences in the characteristics between the subgroups at baseline were tested using one-way ANOVA for normally distributed continuous variables, the Kruskal-Wallis test for non-normally distributed continuous variables, and the chi-square test for categorical variables. For ANOVA the pairwise comparisons were performed using the Tukey HSD test.

2.7 | Ethics statement

In The Netherlands, according to the code of conduct for the use of data in health research (Gedragscode Gezondheidsonderzoek, approved in 2004 by the Dutch College for Protection of Personal Data, taking into account Article 25 of the Dutch Act on the Protection of Personal Data), no ethics committee approval was needed for this research using data from anonymized medical records.

2.8 | Data-sharing and data accessibility

Clinical data from the GIANTT database cannot be made publicly available. Other researchers may extract the data from the GIANTT database and replicate the analysis, provided they follow appropriate governance procedures and have received ethical approval. Interested researchers may contact the GIANTT steering committee (http://giantt.nl/contact.htm) to inquire about accessing the data.

3 | RESULTS

Between January 1, 2007 and December 31, 2013, 40 131 patients with T2DM had been on the GIANTT database for at least 1 year. Treatment with insulin was initiated in 6592 patients. After applying all of the inclusion and exclusion criteria, 1459 patients were selected (Figure 1). The majority of patients (3341) were excluded because they had received less than 2 years of follow-up after insulin initiation. The excluded patients were slightly older, had lower SBP, higher ACR, were less likely to be smokers, and had more comorbidities (data not shown).

The LCGM was performed with one, two, three and four subgroups. The model with four subgroups did not converge. Therefore, the optimal model describes three groups of patients with distinct patterns of change in HbA1c over time. Figure 2 shows the trajectories of HbA1c over 4 years for the three identified subgroups after insulin initiation. HbA1c decreased in all three groups after initiation of insulin, with 68%-70% not achieving the prevailing target level of <53 mmol/mol in the study period. Group 1 consisted of poor responders, with 119 patients showing on average a steadily increasing level of HbA1c after an initial small drop (average HbA1c over the follow-up: 67.1 mmol/mol). In Group 1, HbA1c levels increased from an average baseline level of 60.1 to 73.0 mmol/mol at 2.5 years, after which the number of patients included in the research substantially decreased. Group 2 comprised stable responders, with 1227 patients who had on average a relatively stable level of HbA1c during the follow-up (average HbA1c over the follow-up: 57.2 mmol/mol). Group 3 consisted of initial steep responders, with 113 patients having a high initial HbA1c level (87.9 mmol/mol) at the time of insulin initiation, showing a rapid decline over the first year of follow-up then a small increase during subsequent years of follow-up (average HbA1c over the follow-up: 58.3 mmol/mol).

At baseline, the three subgroups were significantly different with regard to age, diabetes duration, HbA1c level, the number of HbA1c tests, total cholesterol, LDL-cholesterol, triglycerides and eGFR, and the number of patients receiving sulfonylureas (Table 1). The poor responders (Group 1) were significantly younger and more likely to receive sulfonylureas than Group 3 patients. The initial rapid responders with a high baseline level of HbA1c (Group 3) received significantly more tests during the follow-up period, were more likely to have a short diabetes duration (<2 years), and higher levels of total cholesterol, LDL-cholesterol and SBP compared to groups 1 and 2. There were no differences in other oral glucose-regulating drugs at baseline or in the type of insulin initiated.

During follow-up, 72%–86% of patients received an insulin prescription within 90 days before each 6-months period, with the lowest levels recorded for the stable responders (Group 2) (Figure 3A; Appendix S1 [see supporting information]). For the first year and a half the rates of insulin prescribing were slightly higher in the group of initial rapid responders (Group 3). The prescribing of metformin (Figure 3B, Appendix S1) and sulfonylureas (Figure 3C, Appendix S1)

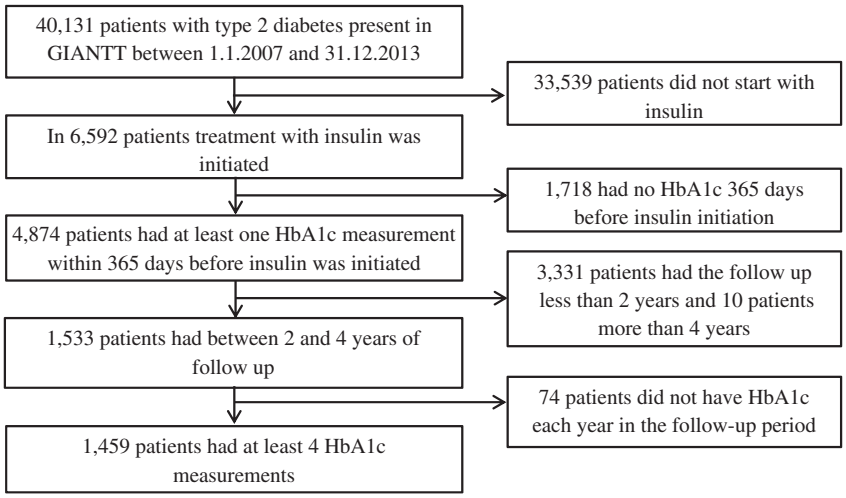

FIGURE 1 Study cohort selection

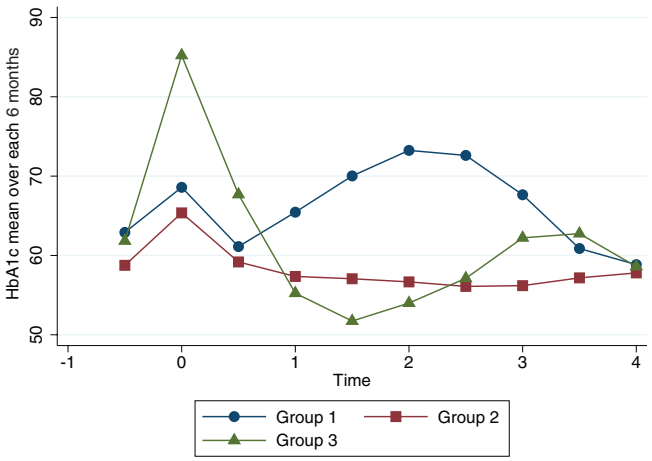

FIGURE 2 Mean-band plot: HbA1c values against time by group. The x-axis is divided into ten six-month intervals and the mean HbA1c is calculated for each interval

decreased in all three groups during the first 2 years after insulin initiation. Patients in the group of initial rapid responders (Group 3) consistently received less co-prescribing of metformin and sulfonylureas than the other groups (Figure 3D, Appendix S1). Patients in the group of poor responders (Group 1) received more co-prescribing of metformin and sulfonylureas in the first 2 years after insulin initiation.

4 | DISCUSSION

Three distinct trajectories of HbA1c were identified in patients with T2DM who initiated insulin in real-life practice. In the majority of patients, HbA1c levels improved during the first year of follow-up and remained stable during subsequent years. In contrast, there was a smaller group (8%) consisting of younger patients with a longer diabetes duration whose HbA1c levels deteriorated, despite a slight improvement at insulin initiation. This group received more co-prescribing of oral drug regimens including metformin and/or sulfonylureas during the follow-up period. Finally, there was another small group (8%) of patients with a shorter diabetes duration and a higher level of risk factors. This group had a very high HbA1c level at baseline which declined rapidly shortly after insulin initiation, but increased thereafter.

The findings of this study are largely in agreement with a previous study looking at HbA1c trajectories after insulin initiation.[9] Both studies clearly show the presence of a small group of poor responders, a small group of rapid responders who had a high HbA1c level at baseline, and a large group of patients with relatively stable HbA1c levels during the follow-up. In addition, Mast et al.[9] identified a fourth group that consisted of patients with a very high HbA1c level at baseline showing a slow improvement in HbA1c levels over time. The absence of a similar group in the current study can be attributed to differences in the studied populations or to differences in the data available for modeling. As previously mentioned, the study by Mast et al.[9] was conducted in a centrally organized care system that differs from the routine primary care system in which the current study was conducted. In this study, with multiple primary care practices there may be significant differences in the timings of insulin initiation. In addition, the HbA1c measurements were more unequally scheduled over time, which may lead to differences in measurement errors in the LCGM modeling.[15]

It is of note that the poor responders in Group 1 in this study were younger and were more likely to receive sulfonylureas at baseline and regimens including metformin and sulfonylureas during the follow-up period. The earlier study on trajectories also reported that poor responders were represented by a relatively younger population.[9] These findings are supported by other studies showing that patients at younger ages have poorer glycaemic control.[16,17] One of the causes for this could be that younger patients may have a more irregular lifestyle and consequently more problems in adhering to treatment with insulin.[18,19] The higher prevalence of patients treated with sulfonylureas in this group may be an indicator of more severe illnesses. During the follow-up period, the poor responders were treated with more intensive regimens including sulfonylureas and metformin. This suggests that the higher HbA1c levels were not caused by clinical inertia, but that non-adherence may be an issue which needs to be addressed in poor responders. In addition, T2DM is seen as a heterogeneous disorder including subgroups which can be clinically characterized, but which also includes less well-defined phenotypes.[20] It is possible that this group of poor responders includes

TABLE 1 Patient characteristics per group at baseline

	All patients	Group 1	Group 2	Group 3
Number of subjects, n	1459	119	1227	113
Follow-up in years, median (IQR)	3.4 [2.7; 3.8]	3.3 [2.7; 3.9]	3.4 [2.7; 3.8]	3.5 [2.7;3.8]
Age in years, mean (SD)	65.6 (12.4)	60.3 (12.9)[a,b]	66.0 (12.1)[a]	66.9 (13.5)[b]
Female, n (%)	776 (53.2)	61 (51.3)	653 (53.2)	62 (54.9)
T2DM duration >2 y, n (%)	1230	106 (89.1)[a]	1044 (85.1)[b]	80 (70.8)[a,b]
HbA1c in mmol/mol, mean (SD)	68.8 (17.2)	70.1 (18.9)[a]	66.9 (14.8)[a,b]	87.9 (25.9)[b]
Number of HbA1c tests, mean (SD)	11.8 (4.1)	11.3 (4.3)[a]	11.8 (4.1)	12.6 (4.1)[a]
Total cholesterol in mmol/L, mean (SD)	4.4 (1.1)	4.3 (0.9)[a]	4.4 (1.1)[a,b]	4.7 (1.1)[b]
HDL-cholesterol in mmol/L, mean (SD)	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)	1.2 (0.4)
LDL-cholesterol in mmol/L, mean (SD)	2.4 (0.9)	2.4 (0.8)[a]	2.4 (0.9)[b]	2.7 (1.1)[a,b]
Triglycerides in mmol/L, mean (SD)	1.9 (1.1)	2.2 (1.4)	1.9 (1.1)	2.2 (1.5)
SBP in mm Hg, mean (SD)	142 (19.6)	141.4 (21.3)[a]	141.5 (18.8)[b]	147.8 (25.3)[a,b]
eGFR in mL/min/1.73 m^2, median (IQR)	75.9 [57.3; 90.3]	85.9 [67.9; 96.8][a,b]	75.0 [56.9; 89.6][a]	73.3 [57.4; 87.9][b]
BMI, mean (SD)	30.6 (5.7)	31.9 (8.0)	30.5 (5.6)	30.7 (6.3)
Micro/macroalbuminuria, n (%)	271 (18.6)	32 (26.9)	210 (17.1)	29 (25.7)
Smoking status, n (%)	184 (12.6)	22 (18.5)	146 (11.9)	16 (14.2)
Insulin type				
Fast-acting, n (%)	42 (2.8)	4 (3.4)	34 (2.8)	4 (3.5)
Intermediate-acting, n (%)	163 (11.2)	11 (9.2)	143 (11.6)	9 (7.9)
Long-acting, n (%)	843 (57.8)	65 (54.6)	704 (57.4)	74 (65.5)
Intermediate- or long-acting combined with fast-acting, n (%)	411 (28.2)	39 (23.8)	346 (28.2)	26 (23.0)
Metformin use, n (%)	955 (65.5)	85 (71.4)	794 (64.7)	76 (67.3)
Sulfonylureas use, n (%)	921 (63.1)	85 (71.4)[a]	775 (63.2)	61 (54)[a]
Acarbose use, n (%)	6 (0.4)	1 (0.8)	4 (0.3)	1 (0.9)
Thiazolidines, n (%)	132 (9.0)	8 (6.7)	118 (9.6)	6 (5.3)
DPP-4 inhibitors, n (%)	66 (4.5)	4 (3.4)	58 (4.7)	4 (3.5)
Other GLDs, n (%)	3 (0.2)	0 (0.0)	3 (0.2)	0 (0.0)
CV morbidity, n (%)	342 (23.4)	23 (19.3)	294 (24)	25 (22.1)
PV morbidity, n (%)	199 (13.6)	20 (16.8)	166 (13.5)	13 (11.5)
Malignancy, n (%)	143 (9.8)	8 (6.7)	128 (10.4)	7 (6.2)
Psych. conditions, n (%)	109 (7.5)	15 (12.6)	86 (7)	8 (7.1)

Abbreviations: BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Psych., psychological; PV, peripheral vascular; SD, standard deviation; T2DM, type 2 diabetes mellitus.

[a,b]Significant differences ($P < 0.05$).

patients with a different disease aetiology and disease progression, which may explain their poorer treatment responses. On the other hand, the group of poor responders was not characterized by a shorter diabetes duration at the time of insulin initiation.

A shorter diabetes duration was observed for the group of patients having very high HbA1c levels at baseline with a rapid response to insulin initiation. This indicates that within this group there are patients who did not respond sufficiently to non-insulin treatment. It could be that these insulin starters with such a short diabetes duration were misclassified, or that they could actually have latent autoimmune diabetes in adults (LADA). Although the records of patients with a diabetes duration of less than 2 years were manually checked to exclude obvious misclassifications, there can be a delay from the date of diagnosis during which patients are not yet treated. Also, it is likely that the healthcare practitioner did not recognize LADA in some of these patients and treated them as patients with T2DM. The shorter diabetes duration may indicate that this group had a larger beta-cell reserve at the time of insulin initiation. Insulin initiation might have counteracted glucose toxicity and stimulated endogenous insulin release, thereby explaining the strong initial response in HbA1c levels. A group of rapid responders with high initial HbA1c levels was also seen in the earlier study on HbA1c trajectories: Mast et al. reported that the rapid response group showed stronger associations with mortality in comparison to the other groups.[9] Further research is needed to determine whether the groups in the current study are also associated with different mortality and complication (e.g. retinopathy) risks. Compared to patients in groups 1 and 2, patients in Group 3 also had higher levels of LDL-cholesterol and SBP. The higher levels of all cardiometabolic risk factors may be an indicator of a more severe disease or suboptimal treatment at the time of insulin initiation, implying that more attention should be given to improving medication treatment and adherence in this group. During

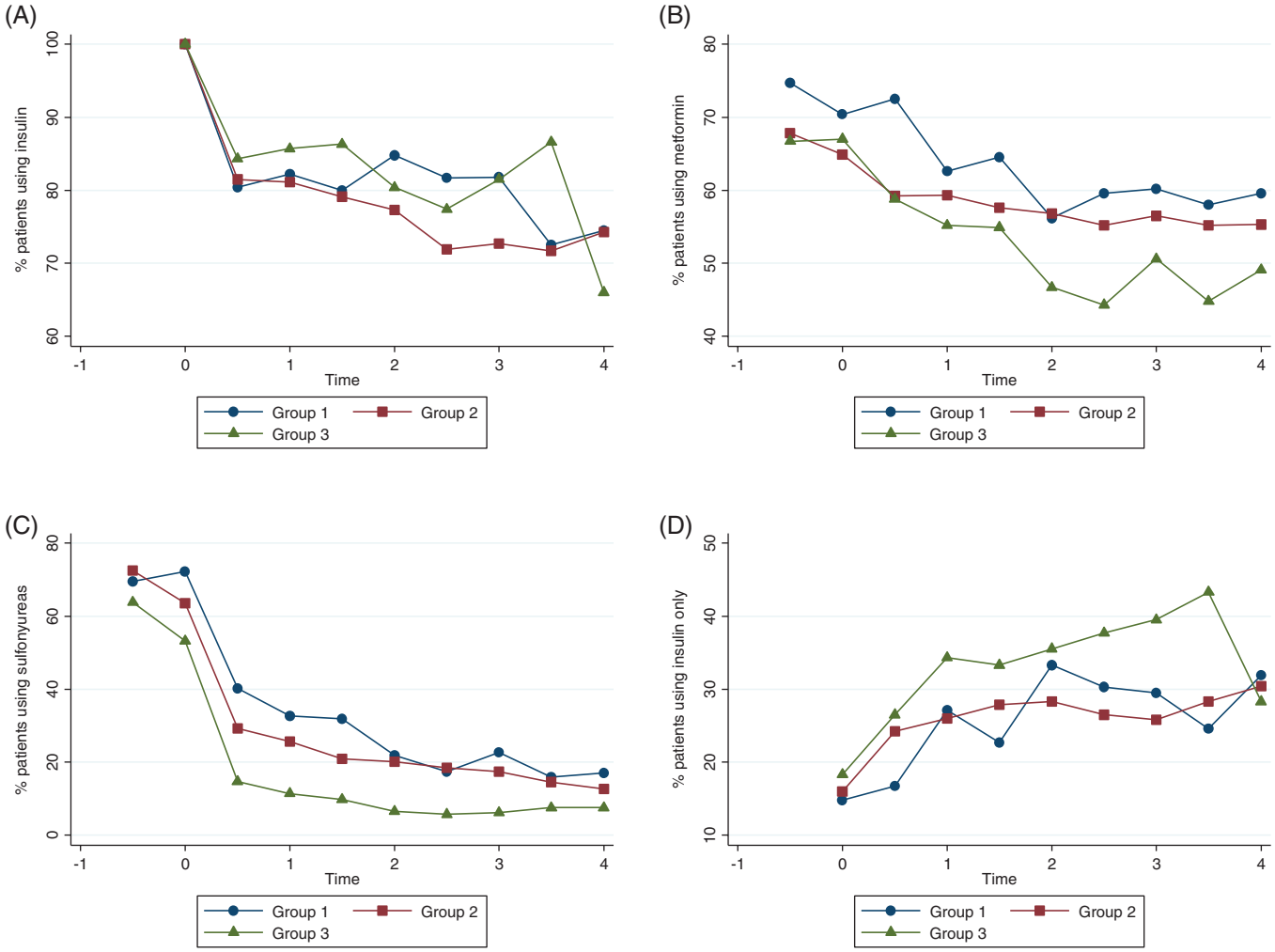

FIGURE 3 Mean-band plot: The percentage of patients prescribed A, insulin, B, metformin, C, sulfonylureas and D, insulin only without co-medication against time by group. The x-axis is divided into ten 6-months intervals and the mean HbA1c is calculated for each interval

follow-up, the patients in this group had slightly more HbA1c tests, which is explained by closer monitoring of patients with very high initial HbA1c levels. However, on average throughout the study period, all of the groups were regularly monitored.

There are a number of earlier studies looking at HbA1c trajectories in general.[21,22] Although these studies did not look at the HbA1c response specifically after insulin initiation, the trajectories of change showed similar patterns. They clearly indicated the presence of a large group of patients with stable HbA1c levels in the follow-up period, a smaller group of patients with high HbA1c levels who appeared to respond well after initiation or intensification of treatment, and another small group of patients whose HbA1c levels deteriorated slowly. This could indicate that there is a subgroup of patients with T2DM who do not respond sufficiently to the currently available glucose-lowering drugs which are prescribed. In the current study, the group of poor responders did not improve, despite higher levels of treatment regimens including metformin and/or sulfonylureas.

The rates of prescribing of insulin and other glucose-lowering drugs varied during the follow-up. The findings show that insulin was not continuously prescribed to all of the patients over time, which is in accordance with earlier studies indicating that many patients have gaps between insulin prescriptions.[23,24] As expected, patients with very high HbA1c levels at baseline were prescribed insulin more frequently within the first year and a half, which corresponded with their rapid decline in HbA1c levels.

A major strength of this study is that it was conducted in a large cohort of patients with T2DM from a routine primary care setting in the north of The Netherlands, and the results are therefore directly relevant for daily clinical practice. However, there are also some limitations to be considered. The population of the GIANTT cohort consists mainly of individuals of western European origins, which may influence the observed levels of HbA1c.[25] Also, because this study analyzes a real life primary-care cohort of patients, the follow-up period was restricted to 4 years. A longer follow-up period would lead to an increased risk of selection bias due to losses during the follow-up. The number of patients included in the study decreased after 3 years of follow-up. This is partly because there are no data covering the third and fourth years of follow-up for patients entering the dynamic cohort after 2010. In addition, some patients may have left the cohort because they died, moved out of the region, were referred to secondary diabetes care, or moved into a care home for the elderly. A wide range of clinical data was included to characterize the different

patient groups. Taking into consideration the data-driven clustering, a prediction model was not constructed. This implies that the significant differences observed between the groups at baseline were not adjusted for the other characteristics. HbA1c values can be inaccurate in patients with anaemia. There were no reliable data to confirm or refute anaemia, but the indications are that anaemia was limited to a specific response group. Finally, the changes in HbA1c can be driven by factors other than insulin initiation, for instance non-adherence to treatment and/or the dosing or intensity of medication treatment. The feasibility of examining the prescribing of other glucose-lowering drugs during the follow-up period was considered, but this was disregarded because it would not be possible to assess insulin doses or non-adherence due to a lack of reliable data. However, patients who discontinued insulin during the follow-up were excluded from the cohort due to the requirement that patients needed at least one insulin prescription within 365 days before each follow-up HbA1c measurement.

In conclusion, this study confirmed the existence of distinct groups of HbA1c trajectories in patients with T2DM initiating insulin in routine primary care. Most patients showed a stable HbA1c response, but one out of six patients showed either a poor response or only a rapid initial response after insulin initiation, associated with age, diabetes duration and risk-factor controls at the time of insulin initiation. Poor responses occurred despite higher levels of co-medication at insulin initiation and during follow-up. The findings emphasize the importance of more personalized care approaches in the process of initiation and management of insulin treatment in patients with T2DM.

Conflict of interest

The authors have declared that no competing interests exist.

Author contributions

G. S., J. F. M. v. B. and P. D. contributed to the study concept and design. G. S., J. F. M. v. B. and P. D. contributed to the acquisition of data. All of the authors contributed to the analysis and interpretation of data. All of the authors contributed to drafting the manuscript. All of the authors contributed to interpretation of the data, reviewing and approving the manuscript prior to submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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